STUDIES ON THE GLUCOCORTICOID RECEPTOR AND THE HORMONAL MODULATION OF THE mRNA FOR TRYPHTOHAN OXYGENASE

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INTRODUCTION

The important role played by steroid hormones in development and physiological regulation in animals has led investigators over the past few decades to attempt to unravel and understand the molecular mechanisms involved in the function of steroid hormones. Several studies have shown that the steroid hormones, including the glucocorticoid hormone, bind with high affinity to specific receptor proteins in the target cell cytoplasm. The glucocorticoid-receptor complex has been shown to undergo an alteration to an "activated" state which has high affinity for chromosomal sites within the cell nucleus. This glucocorticoid-receptor interaction with the genome accompanies, and is presumed to be responsible for, the cellular responses characteristic of the hormone and its target tissues. The receptor proteins promise to be useful probes in understanding genetic control mechanisms and also the organization and structure of the eukaryotic chromosomes.

Considerable information exists concerning the cellular and metabolic alterations evoked by glucocorticoid hormones acting upon responsive tissues. Extensive efforts are now devoted to gaining an understanding of the molecular processes underlying these hormonally-induced alterations. Over the past few years every possible control mechanism has been advocated. These include transcriptional control, translational control, hormone-controlled cytoplasmic, and nuclear receptors and changes in enzymes and mRNA stabilities. The recent and ongoing rapid developments in molecular biology have provided interesting concepts and hypotheses concerning gene expression and its control. Experimental tools that allow direct measurements of cellular parameters, such as measurement of specific species of
mRNA, have been of great value in these studies.

Most of the models proposed to explain the mechanism of glucocorticoid hormone action, are based on the following postulates: (1) the hormone enters the target cells; (2) the target tissues contain receptors; (3) the receptors are located in the cytoplasm and are translocated into the nucleus when complexed with the hormone; and (4) these events are believed to precede and lead to an alteration in the pattern of gene expression. Using the biochemical techniques presently available, the first three of these assumptions have been confirmed. All findings to date, with respect to the glucocorticoid hormones, are compatible with the fourth assumption as well. However, it must be recognized that definitive insight into any of these processes still remains to be established. Ongoing investigations towards understanding the molecular mechanisms involved are focused upon the chemical nature of the cytoplasmic receptor, particularly with respect to its active sites which interact with the steroid hormone and chromatin; the chemistry of the changes in the cytoplasmic steroid-receptor complex as it undergoes "activation;" the processes underlying translocation of the activated cytoplasmic receptor into the nucleus; identification of the specific nuclear sites with which it interacts particularly with respect to the role of the chromosomal proteins and of specific sequences of DNA; a clarification of the molecular events which subsequently ensue in the nucleus concerning the specific hormonally-regulated genes; and a description of the processing of the gene transcript and its ultimate cytoplasmic translation. In this context, this article reviews the recent studies conducted in our laboratory, attempting to elucidate the biochemical processes by which the glucocorticoids regulate the hepatic enzyme levels.

Glucocorticoid Receptor

It is generally accepted that hormones exert their physiologic effects after first combining with specific target cell proteins. In the case of steroids, as originally described for estrogen (Jensen and Jacobson, 1962), these proteins are soluble cytoplasmic components of target tissues capable of interacting with high affinity and stereospecificity for the biologically active steroid. The existence of soluble, intracellular proteins which bind other steroid hormones (i.e., progesterone, aldosterone, dihydroltestosterone) have since been documented. For reviews see Tomkins, Gelehrter, Granner, Martin, Samuels, and Thompson (1969); Feldman, Funder, and Edelman (1972); Jensen and DeSombre (1973); O'Malley and Means (1974); King and Mainwaring (1974). These intracellular steroid hormone-binding proteins are now commonly referred to as "receptors."

Rat liver contains three soluble proteins which bind natural